International Preliminary Examining Authority
European Patent Office
P.B. 5818 Patentlaan 2
N. 2280 HV Rijswijk
Netherlands

8 October 2004

Sent by fax

Dear Sirs

International Patent Application No. PCT/GB03/02459
SOPHION BIOSCIENCE A/S
Our ref: SOPC/P28436PC

This is a response to the written opinion dated 10 August 2004.

We enclose hand-amended pages 27 to 29.

Amendments

Claim 1 has been amended to incorporate the features of claims 4 to 6.

Claim 1 has also been amended to clarify that the electrophysiological change being detected and/or measured in step (iii) is the change in comparison to a control cell. Basis for this amendment can be found on page 5, lines 21 to 24 and page 19, lines 19 to 21.

Finally, Claim 1 has been amended to clarify that the electrophysiological change being detected and/or measured is the result of expression of the heterologous DNA sequence located within each cell. Basis for this amendment can be found on page 5 lines 2 to 3, 10 to 16 and 18 to 21.

In light of the amendment to Claim 1, claims 4 to 6 have been deleted and the remaining claims renumbered accordingly.

Clarity (Art 6 PCT)

The Examiner has objected that Claim 1 does not contain an essential technical feature that is necessary to solve the technical problem that the invention is directed to solving.

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The problem that the invention seeks to solve is clearly indicated on page 1 of the application, namely that screening DNA libraries is normally only directed to investigation of heterologous DNA (i.e. DNA foreign to the cell in which it is located) and/or mRNA or polypeptides derived therefrom.

The amendments to Claim 1 have clarified that Claim 1 does provide a number of features that contribute to solving the technical problems mentioned above:

- Arranging a plurality of cells on the substrate (step (iii)) – this allows many reactions to be conducted at one time, and provides a fast, high-throughput method.
- Study of the cell comprising the heterologous DNA (steps (ii) and (iii)) – this allows the effects of the DNA on the cell as a whole to be assessed.
- Electrophysiology measurements – the electrophysiology of a cell is a cell phenotype that can be influenced by the expression of DNA.

Therefore, the applicant contends that Claim 1 is clear as it adequately discloses features for solving the technical problem.

Novelty (Art 33(2) PCT)

The Examiner has objected that the claims are not novel in light of the disclosure of D1 (WO 02/24862) and D6 (Gehwolf *et al.*).

D1 (WO 02/24862)

D1 relates to a biochip for electrophysiological analysis of cells to which an assay condition is applied.

D1 does not describe the change of electrophysiology in each cell as a comparison of the test cell to a control sample. Instead, page 10, lines 18 to 20 of D1 specifically describes the testing the electrophysiology of the same test cell both before and after exposure to an appropriate assay condition. In the context of the present invention, that assay condition would be the expression of heterologous DNA.

Claim 1 requires the cells to already comprise a heterologous DNA sequence before (step (ii)) they are arranged on test substrate (step (iii)). The present invention does not test the electrophysiology of the same cell before and after

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heterologous DNA expression and the amendment to Claim 1 has clarified that the change detected is in comparison to a control cell.

Hence, D1 does not teach the method of Claim 1 and therefore Claim 1 and all claims dependent therefrom are novel.

D6 (Gehwolf *et al.*)

D6 describes a study of electrophysiological properties of lily pollen protoplasts after rtPCR of mRNA molecules located within the protoplast. The mRNA being studied is membrane H^+ ATPase.

D6 does not describe a number of the features of Claim 1 as amended. D6 does not describe a plurality of cells being arranged on the test substrate, nor does D6 describe a plurality of cells where each cell comprises a different heterologous DNA.

Furthermore, D6 does not describe more than one heterologous DNA sequence. In fact, D6 does not describe any heterologous DNA sequences, as the DNA being studied is a DNA that is already found in the cells being studied.

The purpose of rtPCR in D6 is to amplify DNA from an mRNA molecule that is native to the lily pollen protoplasts. Even though the DNA is present in higher than normal amounts, it does not constitute a heterologous DNA.

Additionally D6 does not describe comparison of the change in the cell of interest as being in relation to a control cell.

The Examiner has also noted in point 3.1, 2nd paragraph of the written opinion, that D6 does not disclose more than one heterologous DNA sequence. As such, the Examiner acknowledges that D6 does not disclose all the features of Claim 1 even prior to amendment.

Therefore, it is clear Claim 1 and all dependent claims therefrom are novel over the disclosure of D6.

Inventive Step (Art 33(3) PCT)

The Examiner believes that D6 is the closest prior art. In light of the discussion regarding D6 for novelty above, the applicant is of the opinion that D6 is considerably different from the present invention and as such, does not represent the closest prior art.

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However, in order to expedite the issuance of a positive International Preliminary Examination Report, the applicant's comments on inventive step are provided below.

D6

The disclosure of D6 is discussed above in relation to novelty.

D6 in combination with D2

D2 is directed to an apparatus for measuring cellular electrical conditions. D2 does not describe the cells being tested as containing heterologous DNA derived from DNA libraries. Furthermore, D2 does not disclose the use of multiple different DNA sequences in each cell (heterologous or otherwise).

As D6 also does not disclose heterologous DNA derived from a DNA library and multiple DNA sequences in different cells, a skilled person could not combine these documents and arrive at the presently claimed invention.

Even if the documents were combined, they also do not disclose that the change in cell electrophysiology is in relation to a control cell.

Therefore, all claims are inventive over a combination of D6 and D2.

D6 in combination with D3

D3 discloses a method of producing a DNA library by high throughput methods and methods of analysing such libraries in order to assign a particular function to each member of the DNA library.

D3 does not provide any indication that electrophysiology measurement techniques might be appropriate in studying the members of the DNA library. In fact, D3 requires a more specific analysis of the function of each DNA library member than electrophysiological measurements can provide.

Electrophysiological measurements can only determine that the heterologous DNA alters a factor that changes the electrophysiology of the cell. However, there are a vast number of factors that influence cell electrophysiology e.g. membrane ion channels (K^+ Na^+ Ca^{2+}, Cl^-), ion pumps (K^+ Na^+ Ca^{2+}, Cl^-), neurotransmitters, enzymes, membrane receptors, G proteins. Introduction of a heterologous DNA could lead to the expression of any one of these factors or even a completely

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separate compound that may act to change cellular electrophysiology in a different manner.

Therefore, measurement of cell electrophysiology can not assign a particular function to a member of a DNA library, as required by D3. Therefore, D3 teaches away from the use of electrophysiology, and as such there is no motivation for the skilled person to combine documents D3 and D6.

Even if the documents were combined, they do not disclose that the change in cell electrophysiology is in relation to a control cell.

Therefore, the claims are inventive over a combination of D6 and D3.

D6 in combination with D4

D4 is directed to methods of modulating gene expression in order to change a cellular phenotype by constructing recombinant polypeptides that disrupt or contribute to gene expression based on a known DNA of known function.

The methods of D4 relate to a different technical field to that of D6. The purpose of D4 is to derive recombinant DNA molecules of unknown function from a DNA molecule of known function, and to investigate whether they have the same function and whether that is up or down-regulated. D4 represents a highly focussed investigation into areas of known function.

By contrast, D6 relates to methods that detect electrophysiological changes in a cell due to heterologous DNA expression. As discussed above, electrophysiological methods are unspecific in their ability to assign particular functions to a cell and represent a less highly focussed investigatory tool.

Due to these documents begin in separate fields; the skilled person would not seek to combine them.

Furthermore, the disclosures of D4 and D6 are incompatible in the focus of their particular investigations (highly focussed in D4 and more general in D6), and therefore there is no motivation for the skilled person to combine these documents.

As such, the claims as amended are inventive over a combination of D4 and D6.

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D6 in combination with D5

D5 is directed to methods of screening calcium channel modulators by contacting the calcium channel with the activator and determining the activity of the channel.

D5 does not disclose the use of DNA libraries and certainly does not describe the use of multiple heterologous DNA sequences. In fact, D5 only discloses the presence of one heterologous DNA sequence, the reporter gene, and this is introduced into each cell being studied.

In light of D6 also not disclosing DNA libraries and not describing the use of multiple heterologous DNA sequences, a combination of D5 and D6 could not result in the present invention.

As such, all claims are inventive over a combination of D6 with D5.

Further possible combinations

As discussed above, there is no motivation to combine any of documents D2, D3, D4 or D5 with D6 as no combination provides all the features of the present invention.

Additionally, a skilled person would not be motivated to further combine three documents, e.g. D6, D5 and D3, as they would already have determined that a combination of either D6 and D5 or D6 and D3 would not provide a beneficial result that solves the technical problem.

As such, the present claims are inventive over all combinations of the cited documents.

Any amendment is not to be construed as abandonment of subject matter.

Yours faithfully
ERIC POTTER CLARKSON

Helen Johnstone

jw/sjc

Enc: Hand-amended pages 27 to 29 (x 3)